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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/032,996
Filing Date: December 27, 2001
Appellant(s): BOTSTEIN ET AL.

AnneMarie Kaiser
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 23, 2005 appealing from the Office action mailed April 25, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Appellant has identified 10/033,396 as a related appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Rost, B. "Enzyme function less conserved than anticipated", J. Molecular Biology, vol. 318 (2002), pp. 595-608.

Konopka et al. "Variable expression of the translocated c-abl oncogene in Philadelphia chromosome positive B-lymphoid cell lines from chronic myelogenous leukemia patients" Proc. Natl. Acad. Sci., vol. 83 (June 1986), pp. 4049-4052.

Pennica et al. "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1 transformed cells and aberrantly expressed in human colon tumors" Proc. Natl. Acad. Sci., vol. 95 (December 1998), pp. 14717-14722.

Meric et al. "Translation initiation in cancer: A novel target for therapy" Molecular Cancer Therapeutics vol. 1 (September 2002), pp. 971-979.

Gokmen-Polar et al. "Elevated protein kinase C BII is an early promotive event in colon carcinogenesis" Cancer Research, vol. 61 (15 February 2001), pp. 1375-1381.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27-35, 37-40 and 46-54 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a genus of nucleic acids which encode a protein termed Pro-539 (SEQ ID NO: 7) or portions thereof, in the specification, which have at least 95% amino acid sequence identity to SEQ ID NO: 7.

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the proteins. The cited utilities in the specification include overexpression in cancer. These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the PRO 539 polypeptide. A review of the specification and of the prior art finds no well established utilities for unknown proteins whose activity, whose enzymatic or other biochemical function and whose cellular roles are entirely unknown and undisclosed in the specification.

The next inquiry is whether there are substantial or specific utilities for the PRO 539 protein of SEQ ID NO: 7 which are identified in either the specification or in the prior art.

Substantial utility

Here, the evidence in the specification provided is that the nucleic acid which encodes the PRO 539 protein is overexpressed in cancer cells. The level of overexpression of PRO 539 was minimal, not even a two fold overexpression in any cell type. Further, no statistical data was presented to show that the overexpression was significant in any way, with no P-value or other statistical measure to demonstrate that the overexpression was a real effect and not simply produced by chance.

This data further lacks any of the hallmarks of utility because the overexpression of the nucleic acid is not relevant to the utility of the protein. There is no evidence that the protein itself is overexpressed. Meric et al (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein.

The absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar (Cancer Research (2001) 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isozyme expression is likely regulated at the posttranscriptional/translational level (see abstract)." Gokman-Polar show in figures 6 and 7 that there is no increase in mRNA expression for any of the isozymes, while the protein is significantly overexpressed as shown by figures 4 and 5. This demonstrates that there is no relationship between mRNA levels and protein levels.

A further evidentiary showing is provided by Pennica et al (Proc. Natl. Acad. Sci. USA (1998) 95:14717-14722) who shows that WISP-2 DNA was amplified in cancer cells but was actually demonstrated REDUCED RNA expression (see abstract). This provides additional evidence that there is no relationship between gene amplification

and mRNA levels, since mRNA levels have no necessary correlation with gene amplification.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself.

Further, given the breadth of these claims which encompass 95% identical molecules, there is an abundance of evidence that very similar proteins can perform very different functions. For example, Rost et al (J. Mol. Biol. (2002) 318(2):595-608) notes regarding assignment of enzymatic activity based upon homology comparisons that "The results illustrated how difficult it is to assess the conservation of protein function and to guarantee error-free genome annotations, in general: sets with millions of pair comparisons might not suffice to arrive at statistically significant conclusions (abstract)." Thus, even high levels of homology do not necessarily correlate with actual protein function. In the current case, where the function of PRO-539 (SEQ ID NO: 7) is not known, the expectation is even lower that there is any utility that can be derived based upon the sequence.

This situation is extremely similar to example 12 of the Utility Guidelines, where a protein which was known to be a receptor, but where the ligand was unknown, was found to lack utility. In the current case, the putative PRO-539 protein, lacks any substantial utility whatsoever, and solely relies upon an small level of mRNA

overexpression in cancer cells. However, there is no necessary relationship between the protein levels or utilities and such an overexpression of the nucleic acid. So this case is similar to the receptor in Example 12, since it lacks a substantial utility because there is no "real world" context of use. Further research would be required to identify and reasonably confirm a "real world" context of use for PRO-539. As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials).

Specific Utility

In the current case, even if the substantial utility argument above were found unpersuasive, there is no specific utility given for this PRO-539 protein of SEQ ID NO: 7. The protein, as distinguished from the nucleic acid, has not been associated with any disease, any condition, or any other specific feature. There is no association of the protein with cancer or with any other disease. As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed". Here, the overexpression of the nucleic acid gives no specific utility because it is entirely unrelated to uses of the protein. A protein cannot be used to detect changes in its cognate nucleic acid, as shown by the Gokman-Polar and Meric papers, where protein levels are not correlative with nucleic acid levels. Therefore, there is no specific utility for this protein until a specific ligand is identified.

Finally, with regard to the utility analysis, the current situation directly tracks Examples 4 and 12 of the utility guidelines, where a protein of entirely unknown function and a receptor with an unknown ligand was characterized as lacking utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 37-40 and 46-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of proteins which are different from those disclosed in the specification, since the claims are not limited to any particular

SEQ ID NO, but are open to a protein that ranges from 95% to 99% identical to SEQ ID NO: 7, without any guidance on conserved portions of the protein structure.

Most significantly, the genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named SEQ ID No 7. Thus, applicant has express possession of only one particular amino acid sequence in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains.

There is no showing or evidence which links structural limitations or requirements to any particular functional limitations. Further, these claims encompass alternately spliced versions of the proteins, allelic variants including insertions and mutations, inactive precursor proteins which have a removable amino terminal end, and only specific nucleic and amino acid sequences have been provided. No written description of alleles, of upstream or downstream regions containing additional sequence, or of alternative splice variants has been provided in the specification.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one

> might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the nucleic acids as having 95%-99% sequence identity to SEQ ID NO: 7 lacks any specific structure, since it lacks the correlation between structure and function that is at the heart of the caselaw and of the written description guidelines.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound without identifying the structure function relationship of the compound, so that the compound is claimed solely its protein sequence related 80%-99% to SEQ ID NO: 7 without any correlative function to delimit the structure.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any proteins other than those expressly disclosed which comprise SEQ ID NO 7. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 112 – Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-35, 37-40 and 46-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a PRO-539 protein which is 95-100% identical to SEQ ID NO: 7. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims broadly encompass not only the particular PRO-539 protein but also include any protein which shares 95% sequence identity to SEQ ID NO: 7.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity of polypeptides and nucleic acids. It would require significant study to identify the actual function of the PRO-539 protein and nucleic acid, and identifying a use for this protein would be an inventive, unpredictable and difficult undertaking in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is extremely unpredictable with regard to protein function in the absence of reliable information regarding the protein activity. Even very similar proteins, as shown by homology, may have very different functions (see Rost et al (J. Mol. Biol. (2002) 318(2):595-608). In the current case, where no specific information is known regarding the function of the protein in actual biological organisms, it is entirely

unpredictable what function and activity will be found for this protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the protein.

This data further lacks any of the hallmarks of utility or of any enabled use because the overexpression of the nucleic acid is not relevant to the utility of the protein. There is no evidence that the protein itself is overexpressed. Meric et al (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein.

The absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar (Cancer Research (2001) 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isozyme expression is likely regulated at the posttranscriptional/translational level (see abstract)." Gokman-Polar show in figures 6 and 7 that there is no increase in mRNA expression for any of the isozymes, while the protein is significantly overexpressed as shown by figures 4 and 5. This demonstrates that there is no relationship between mRNA levels and protein levels.

A further evidentiary showing is provided by Pennica et al (Proc. Natl. Acad. Sci. USA (1998) 95:14717-14722) who shows that WISP-2 DNA was amplified in cancer cells but was actually demonstrated REDUCED RNA expression (see abstract). This provides additional evidence that there is no relationship between gene amplification and mRNA levels, since mRNA levels have no necessary correlation with gene amplification.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself.

So it is entirely unpredictable how one would use this protein in any context whatsoever.

Working Examples

The specification has no working examples that relate to the protein. The nucleic acid working examples, showing overexpression in certain cancer cell lines, are not relevant for the reasons given above. Specifically, there is no statistical showing that the overexpression of the nucleic acids is even significant in any way. Even if the nucleic acid data is deemed significant, there is no showing that the results from nucleic acids have any correlation with the protein and the art cited above demonstrates that there is no presumption of such a correlation..

Guidance in the Specification.

The specification provides no specific or substantial uses for the PRO-539 protein. The specification does generically teach that the protein may be used in further research, such as in generation of antibodies, but provides no specific and substantial use for the protein.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

(10) Response to Argument

Utility/Enablement rejection

The utility analysis below begins with a basic factual analysis of the evidence supporting a utility for the protein of PRO539, then proceeds to the legal analysis of this utility. However, the claims are not drawn to nucleic acid so even if the Board disagrees and finds that the nucleic acid has utility, the issue is whether this utility carries over into a speculative protein that might or might not exist and might or might not be expressed or overexpressed by the PRO6182 protein.

Factual Predicate underlying Utility Determination

Before any analysis of the legal elements of substantial and specific utility can be applied to the protein named PRO539, the supporting evidence for utility must be identified. In the brief at page 10 matter, Appellant argues for utility by noting that in Example 16 "Appellants disclose that the gene encoding PRO539 mRNA is amplified at least 2 fold in a majority of lung and colon tumors tested compared to normal tissue, respectively" and citing to pages 108-114 of the specification. The table on page 117 of the specification demonstrates that unlike the other tested mRNAs, PRO539 never exceeded a CT value of 2 and apparently was only overexpressed in less than half the samples tested.

Appellant characterizes the assay as being capable of quantitatively measuring the level of gene amplification in a sample. Appellant asserts that gene amplification is an essential mechanism for oncogene activation. Appellant reviews how the assay was performed, and reports that the gene encoding PRO539 was significantly amplified

(never with a CT greater than 1.94 and every sample having CT of 1.32 or less) in eleven samples. This has been fully considered but is not found to be persuasive. First, it is important to note that the gene encoding PRO539 was not found to be amplified in twenty-two other listed tumor samples. Also, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (bottom of p. 115). The art uses matched tissue samples as the standard in such cases (see Pennica et al., Konopka et al.). This is especially important in lung, since the art shows that both cancerous and non-cancerous lung tissue can be aneuploidy. Given these details, one skilled in the art would not conclude that the gene encoding PRO539 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Furthermore, the data pertaining to gene amplification do not convey utility to the claimed polypeptides, since a small amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA and polypeptide levels (see Pennica et al., Konopka et al., Gokman-Polar.).

There is no evidence in the specification that the protein is overexpressed. There is, in fact, no evidence that any protein encoded by PRO539 is expressed in any tissue under any circumstances. The protein encoded by PRO539 may never be expressed and may not be part of the human proteome. The utility of these claims to protein PRO539 rely entirely upon speculation that amplification of the gene of PRO539 results in amplified expression of an mRNA which is then expressed into the deduced amino acid sequence of the protein and that this protein further will be overexpressed in

concordance with the mRNA which will be amplified in concordance with the amplified gene.

Appellant heaps one speculation on top of another, speculating first that the lung tumor samples are representative of all lung tumors, that the amplification of the gene will necessarily result in overexpression of the mRNA. This mRNA speculation must then support the further speculation, without any evidence whatsoever in the specification or declarations, that the PRO539 protein shares the mRNA utility, when the protein may or may not exist, and if in existence, may or may not be overexpressed. This absence of evidentiary support, along with the substantial evidence provided by references such as Pennica, Meric, Gokman-Polar and Konopka, is the predicate for the current utility rejection.

Legal Analysis

Brenner

In analyzing utility, the first place to begin is with the decision of the Supreme Court in Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (1966). In Brenner, the Court concluded that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field." Id. at 534-35, 148 USPQ at 695.

There is no specific benefit, in currently available form, for the Pro-539 protein or antibody, since there are no specific and substantial utilities for that Pro-539 protein or antibody.

Kirk

The CCPA first applied Brenner in In re Kirk, 376 F.2d 936, 153 USPQ 48 (CCPA 1967). The invention claimed in Kirk was a set of steroid derivatives said to have valuable biological properties and to be of value "in the furtherance of steroidal research and in the application of steroidal materials to veterinary or medical practice." Id. at 938, 153 USPQ at 50. The claims had been rejected for lack of utility. In response, the applicants submitted an affidavit which purportedly "show[ed] that one skilled in the art would be able to determine the biological uses of the claimed compounds by routine tests." Id. at 939, 153 USPQ at 51.

The court held that "nebulous expressions [like] 'biological activity' or 'biological properties'" did not adequately convey how to use the claimed compounds. Id. at 941, 153 USPQ at 52. Nor did the applicants' affidavit help their case: "the sum and substance of the affidavit appear[ed] to be that one of ordinary skill in the art would know 'how to use' the compounds to find out in the first instance whether the compounds are—or are not—in fact useful or possess useful properties, and to ascertain what those properties are." Id. at 942, 153 USPQ at 53.

The Kirk court held that an earlier CCPA decision, holding that a chemical compound meets the requirements of § 101 if it is useful to chemists doing research on steroids, had effectively been overruled by Brenner. "There can be no doubt that the

insubstantial, superficial nature of vague, general disclosures or arguments of 'useful in research' or 'useful as building blocks of value to the researcher' was recognized, and clearly rejected, by the Supreme Court" in Brenner. See Kirk, 376 F.2d at 945, 153 USPQ at 55.

The current situation is identical to that in Kirk. The Declarations filed provide evidence that one could determine whether the Pro-539 protein is useful, but do not even show any utility specifically for the claimed Pro-539 protein as discussed above. Further, the discussion cited by Applicant of the various declarations clearly represent language which is "useful in research" but has no current practical use. The speculation by the Declarants that medical practitioners might wish to know if proteins in general are overexpressed, without reference to Pro-539 in particular, is precisely the sort of vague argument which lacks any specificity.

Fisher

The Fisher appellant argued that EST expression during anthesis supported a finding of utility since the protein would be expressed. This utility is highly similar to the current utility since both are based upon relative expression of mRNA in a tissue. The only difference is that the Fisher appellant was actually claiming the mRNA while the current Appellant is claiming the protein which may or may not result from the mRNA that may or may not be expressed from the amplified gene, and if present, may or may not have been overexpressed and if overexpressed, may or may not yield the protein which itself may or may not be overexpressed. The Federal Circuit rejected this argument at page 15 of the decision (as posted on the Federal Circuit Web site), noting

that no evidence of the claimed expression, which was shared in common with 2000 molecules, was provided in the specification. That is virtually identical to the current case, where Appellant argues that PRO539 protein is overexpressed without any evidence of such claim expression. Appellant argues that this provides utility for the nucleic acid, without any evidence that of the function or use (or even evidence of existence) of the protein encoded by PRO6182. No evidence whatsoever was presented that regarding the function of the claimed PRO539 protein molecule or mRNA molecule, only speculation on the activity based upon the amplified genomic DNA of PRO539.

The Federal Circuit than cited the Kirk decision,

> "We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates."
>
> 376 F.2d at 942 (emphasis added).

Further, the Federal Circuit commented that Fisher failed to provide any evidence - test data, declaration, deposition testimony or otherwise - to support the uses argued as presently beneficial and practical. This same fact pattern applies to the current case. There is no test data, declaration, deposition testimony or any other evidence which supports any particular specific and substantial use for the *protein* of PRO539. The only test data is represented by limited, preliminary data which shows, at best, that the PRO539 gene is amplified in a subset of tumors. There is no evidence that this data

has statistical significance or can be used in even unreliable assays to diagnose any cancer or disease whatsoever.

Prima Facie Case

Appellant challenges whether the rejection presents a prima facie case. There has been a spectrum of evidence present in the decisional law of the Federal Circuit. At the low end, in Fisher, neither the applicant nor the examiner provided any references or data on utility, and the absence of any data supporting utility led to a finding that the ESTs lacked utility. The Federal Circuit cited three cases, Jolles, Nelson and Cross in the Fisher decision, each of which had much more evidence of utility. In Jolles and Nelson, there was in vivo animal data that the compounds were effective and in Cross there was specific in vitro data showing effectiveness. In each of these cases, there was no evidence presented which served to rebut utility. The current case falls between these situations. Appellant has presented some data regarding utility in the specification and has provided several declarations. However, there is also significant evidence cited which rebuts Appellant's arguments, particularly with regard to the issue of "necessary" or "statistical certainty".

The issue is whether the evidence presented shows that "more likely than not", the claimed PRO539 protein would have the argued utility of functioning as a diagnostic. It is the protein which is being claimed. No direct evidence is presented with regard to the PRO539 protein in the specification or declarations. Indeed, as noted above, no evidence is presented that this protein actually exists, and certainly no evidence of its expression pattern in any cell type is presented.

Stepping back to Appellant's data in the specification, table 6 at page 114 shows that 36 different tumor samples were tested. Table 7 at page 117 shows that there was "amplification" of PRO539 in 11 samples. In a simple sense then, the specification itself evidences the fact that it is more likely than not true that any particular tumor sample will NOT be associated with a tumor. That is, 25 out of 36 times, PRO539 nucleic acid was NOT associated with a tumor in Appellant's own specification. The evidence therefore shows that the PRO539 nucleic acid normally lacks any association with tumors.

However, the prima facie case does not stop there. The rejection cites specific evidence, in the form of prior art, such as Meric, Gokman-Polar and Pennica, which show that there is no necessary correlation between nucleic acid levels and protein levels. Even Appellant's own cited art, such as Orntoft and Hyman demonstrate that nucleic acid and protein levels are not necessarily correlated. As Orntoft notes "A poor correlation between mRNA and protein levels was found in liver cells as determined by arrays and 2D page (see page 44, column 2)." Appellant's attempt to rebut this argument with the Polakis declaration. It is important to realize that Appellant's entire argument is based upon the speculation, without any direct evidence for the protein of PRO539 whatsoever, that because the PRO539 nucleic acid is amplified in 11 out 36 tumors, the mRNA expressed from that nucleic acid will also be amplified, and the claimed PRO539 protein ultimately translated from that mRNA will be amplified. Specific evidence has been presented to show that this chain of causality is unpredictable and that there is no expectation with regard to any particular molecule. Indeed, the Polakis declaration supports this unpredictability when Dr. Polakis notes

that 20% of the time in his own experiments there is no protein overexpression correlated with mRNA expression. This evidence provides a prima facie case that utility is lacking.

As a side comment, Appellant refers to the related 10/033,167 application in which the nucleic acid of PRO539 was allowed. This demonstrates the care with which this analysis proceeds. The evidence for the nucleic acid overexpression, while weak, does not rise to the speculative levels necessary for the protein or antibody claims.

The evidence, as a whole, does not support PRO539 protein overexpression

Appellant attacks the Meric reference by arguing the word "necessary". This is the central question. Is it inevitable, or at least more likely than not, that PRO539 protein is overexpressed (and therefore presumably useful as a diagnostic) solely because there is a two fold overexpression of the genomic DNA. Meric supports the conclusion that this is not a "necessary" result. When Appellant argues that "statistical certainty" is not required for utility, that is clearly correct. However, the complete absence of any supporting data at all is much closer to the Fisher situation, than to Nelson or the other cases in which direct evidence was presented. As Federal circuit notes in Fisher,

> "Moreover, all of Fisher's asserted uses represent merely hypothetical possibilities, objectives which the claimed ESTs, or any EST for that matter, could possibly achieve, but none for which they have been used in the real world. Focusing on the two uses emphasized by Fisher at oral argument, Fisher maintains that the claimed ESTs could be used to identify polymorphisms or to isolate promoters. Nevertheless, in the face of a utility rejection, Fisher has not presented any evidence, as the Board well noted, showing that

> the claimed ESTs have been used in either way." In re Fisher, 76 USPQ2d 1225, 1231, 1232 (Fed. Cir. 2005).

The current situation is precisely the same as in Fisher. Appellants asserted diagnostic use for the protein of PRO539 represents a mere hypothetical possibility. As in Fisher, the current Appellant has presented no evidence that the protein of PRO539 has any diagnostic use. The Federal Circuit decided that the ESTs lacked utility for the same reason that the protein of PRO539 lacks utility, because no substantial or specific utility, or practical "real world" utility was supported by evidence.

Appellant also attacks the Gokman-Polar and Pennica et al. et al. references relied upon by the examiner. Appellant argues that Gokman-Polar does not support the argument because the protein is overexpressed where the mRNA is unchanged. Gokman-Polar is cited to demonstrate that mRNA levels and protein levels are not necessarily connected, which is the central point upon which Appellant must rely to support the utiliyt of the protein of PRO539. Without such a direct linkage, there would be no expectation of a diagnostic utility for the protein of PRO539. Gokman-Polar further evidences that no such direct linkage exists. Further, Appellant characterizes Pennica et al. as being limited to WISP genes, and does not speak to the correlation of gene amplification and protein expression for genes in general. Appellant argues that the working hypothesis among those skilled in the art is that there is a correlation between gene amplification and protein overexpression. Appellant points out that there was such a correlation for WISP-1 as disclosed by Pennica et al. Appellant characterizes Konopka et al. as being limited to the abl gene, and not speaking to genes in general. Appellant concludes that the examiner must show evidence that it is

more likely than not that the correlation does not exist, and that a *prima facie* case of lack of utility has not been made. This has been fully considered but is not found to be persuasive. Pennica et al. and Gokman-Polar et al. are relevant even though they are not reviews of gene amplification for genes in general because they show a lack of correlation between gene amplification and gene product overexpression. The instant case also concerns a single gene. Moreover, the rejection is based on more evidence than just Pennica et al. and Konopka et al. The evidence of record indicates that (1) the initial gene amplification assay only showed a positive result for eleven out of 36 cancer samples, and did not take into account aneuploidy in cancerous and non-cancerous lung tissue (lack of matched tissue sample control, lack of aneuploidy control), (2) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), and (3) increased mRNA levels do not reliably correlate with increased polypeptide levels in the majority of cases (Orntoft).

Appellant argues that knowledge of the function of the protein is irrelevant. Appellant's lack of knowledge of any function for the PRO539 protein is directly relevant because it shows that there is no other possible utility for the PRO539 protein other than the argued diagnostic utility. If the diagnostic utility is found insufficient, there is no other utility present.

Examples 4 and 12 support the utility rejection

Appellant takes issue with the reliance on Examples 4 and 12 of the Utility guidelines. Appellant states that "In contrast to Examples 4 and 12, in the instant case the specification teaches that the gene encoding the PRO539 protein is amplified at

least two-fold in the majority of lung and colon tumors tested." First, as a factual matter, the gene is not amplified in a majority of the tumors tested as discussed above. Second, Example 4 is specifically interested in proteins which for which no function is provided and no description of the chemical, physical or biological properties other than sequence is given. That is the precise case here. The amplification of the PRO539 nucleic acid imparts no function or chemical, physical or biological properties to the PRO539 protein. No properties are known and therefore, following the logic of Example 4, PRO539 lacks utility.

Similarly, Example 12 also deals with uncharacterized proteins and the result is the same as Example 4. Without specific evidence supporting a utility for the specific molecule claimed, the utility rejection is indicated as required by the Utility guidelines.

Specific Utility arguments for protein

Appellant is not, however, claiming a nucleic acid or mRNA, but rather a protein. So further speculation by Appellant is required to presume that the protein expressed by the mRNA of PRO539 would share the diagnostic utility of the mRNA, without any evidence whatsoever. This is the Fisher situation described above exactly. It is important to reemphasize that the protein of PRO539 is never demonstrated by Appellant to be expressed at all, much less overexpressed in tumors. There is no evidence whatsoever with regard to PRO539 protein.

Appellant begins by citing the Alitalo, Genes V, Merlino, Orntoft, Hyman, Pollack, Bahnassy and Blancato references. None of these references demonstrate anything specific regarding PRO539. References such as Genes V appear entirely irrelevant,

since they provide no evidence that the protein which results from the mRNA encoded by the amplified gene is overexpressed. Further, some of these references actually support the conclusion in the rejection. Orntoft notes "A poor correlation between mRNA and protein levels was found in liver cells as determined by arrays and 2D page (see page 44, column 2)."

Hyman et al. found 44% (less than half) of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. This is direct evidence that it is "more likely than not" that gene amplification does not correlate with increased mRNA expression. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; 2% does not provide a reasonable expectation that the slight amplification of PRO341 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression.

The Pollack reference also supports the rejection, when Pollack notes that only 62% of amplified genes were associated with increased mRNA expression levels and that only 42% of genes were associated with large changes in mRNA expression (see page 12966, column 1). This demonstrates that it is "more likely than not that" that genes that are amplified are NOT associated with large changes in mRNA expression and the mRNA expression is therefore not likely to function as a surrogate for diagnosis of cancer. Further, this analysis does not even reach down to the protein level.

The Smith declaration and these references do not disturb the prima facie case of lack of utility. In fact, the Smith declaration actually supports the conclusion in the rejection. Dr. Smith shows that out of twenty six lung tumor samples, PRO539 is overexpressed in eight. This shows that looking at any particular lung tumor sample, it is "more likely than not" that the mRNA of PRO539 will not be coordinately expressed with any particular amplification. Dr. Smith's conclusion regarding the protein levels for PRO539 is simply speculation without evidentiary support. Further, in 18 of the samples, no mRNA overexpression is found.

Appellant argues that the rejection relies upon a single contrary example in Pennica. This is not correct. There are many contrary examples, where mRNA expression is not correlated to amplification and protein expression is not correlated to mRNA expression, as shown in Orntoft, the Smith declaration itself, the Polakis declaration itself, Meric and Gokman-Polar. There is no evidence that the protein itself is overexpressed. Meric et al (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein. Second, the absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar (Cancer Research (2001) 61:1375-1381) who

teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isozyme expression is likely regulated at the posttranscriptional/translational level (see abstract)." Gokman-Polar show in figures 6 and 7 that there is no increase in mRNA expression for any of the isozymes, while the protein is significantly overexpressed as shown by figures 4 and 5. This demonstrates that there is no relationship between mRNA levels and protein levels.

While undoubtedly many additional references could be adduced to further demonstrate this point, the central issue is the specific nature of the utility for the PRO539 protein. No evidence is presented that this protein has the diagnostic utility which Appellant claims. There is substantial evidence that the argued utility is not inherent based upon the amplification of the PRO539 gene or even the less than 50% of the time that the mRNA is overexpressed.

Appellant then relies upon the Grimaldi, Smith and Polakis declarations. Grimaldi and Smith simply expresses an opinion, which is given that level of weight, relative to the evidence of Pennica, Meric and Gokman-Polar papers, among other references. With regard to the Polakis declaration, it is important to note that Dr. Polakis clearly states that a variety of scientific techniques, including microarray analysis, have been used for detecting and studying differential gene expression in human tumor cells relative to normal cells at genomic DNA, mRNA, and protein levels. Dr. Polakis does not state that microarray analysis ***alone*** can establish the use of a polypeptide as a diagnostic marker for a specific tumor. In fact, the art teaches the

results obtained from microarray analysis require confirmation by independent methods, such as northern blot analysis and Western blot analysis (see, e.g., Pennica and Konopka). Secondly, Dr. Polakis states approximately 80% samples show correlation between increased mRNA levels and *changes* in the level of protein expressed from that mRNA. One of skill in the art would understand that changes in the level of protein means either an increase or a decrease. Thus, the declaration of Dr. Polakis does not support Appellant's assertion that increased mRNA levels correlate increased protein levels.

Thirdly, Dr. Polakis states that approximately 200 genes transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis does not state that how many proteins encoded by the 200 genes are expressed at significantly higher levels than in corresponding normal human cells. Dr. Polakis states antibodies to about 30 of the tumor antigen proteins have been developed and used to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Dr. Polakis does not state that the 30 of "tumor antigen proteins" are expressed at significantly higher levels than in corresponding normal human cells.

Moreover, the declaration does not provide data such that the Examiner can independently analyze and draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoding polypeptide. In fact, the art

teaches the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (Pennica and Konopka). It is noted that while the absolute certainty is not the legal standard for utility, a specific and substantial utility is required for the claimed invention.

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not increased mRNA levels are predictive of increased polypeptide levels. (2) The art provides strong evidence that increased mRNA levels do not correlate with increased protein levels in both healthy and cancerous tissues. See Pennica and Konopka. (3) Dr. Polakis has an interest in the case since he is employed by the assignee. Finally, (4) while Dr. Polakis bases his findings with reference to facts, the facts are not independently provided for the examiner to draw independent conclusions. For example, it is not clear if any of the tumors were from lung, or how highly amplified the genes were that correlated with polypeptide overexpression. Based on the totality of the evidence, considering it anew, it is maintained that one skilled in the art would view the instant gene amplification data as merely preliminary with regard to whether or not mRNA or protein levels of PRO539 are specifically amplified in lung tumors. Further research would have to be done in order to determine if PRO539 mRNA and protein are amplified and, if so, whether or not the amplification is significant enough to reasonably

confirm the usefulness of PRO539 protein as a lung cancer marker. Thus, the claimed invention does not provide products or services in "currently available" to the public, and the asserted utility is not specific or substantial.

Importantly, none of these analyzed genes of Dr. Polakis appear to be PRO539. Thus, the argument is framed by Appellant entirely in generalities. No specific utility is shown for the protein encoded by PRO539.

Recap of Decisional Law

Appellant reargues the decisional law discussed above. As discussed above, when comparing this case to Fisher, Nelson, Cross and Fujikawa, certain trends can be discerned. In each of the cases cited where utility was found, in vitro (and more often in vivo) testing of the specific molecule of interest demonstrated that the specific molecule functioned in a specific assay. As the Federal Circuit noted with regard to these cases when discussing them in Fisher, "In Jolles, Nelson, and Cross, the applicants disclosed specific pharmaceutical uses in humans for the claimed compounds and supported those uses with specific animal test data, in vitro, in vivo, or both." Fisher at 1234. Fujikawa also represents a situation where the specific compounds being claimed were tested for in vitro function and showed such function. See Fujikawa v. Wattanasin 39 USPQ2d 1895, 1900 (Fed. Cir. 1996). That contrasts significantly with the current case where there is no specific test for the claimed protein. Applicant first cites Fujikawa v. Wattanasin for the proposition that utility need be shown only to a "reasonable certainty" and absolute proof is not required. This argument is not persuasive for two reasons. First, as evidenced by the art such as Pennica and Konopka, even if the the

"reasonable probability" standard is used, there is no reasonable certainty that a protein will be overexpressed when the nucleic acid is expressed.

Second, and perhaps more importantly, the case is really inapposite to the current situation because the utility question is significantly different. In Fujikawa v. Wattanasin, the question was whether in vitro testing that showed a compound lowered cholesterol provided utility for that compound as confirmed by in vivo testing. In the current case, no in vivo results whatsoever are present. The use of the Fujikawa compound is expressly evident from the results, that is, the compound can be used to treat high cholesterol, and that is the use intended by that applicant. That situation is significantly different from the current case because there is no evidence that the Pro-539 protein is diagnostic of cancer. Unlike the in vitro testing in Fujikawa v. Wattanasin, where a positive result provided an indication that the compound was potentially useful in cholesterol lowering, and which result was confirmed by in vivo testing, a positive result of overexpression in lung cancer for the Pro-539 nucleic acid provides very little information for utility of the nucleic acid. There is no "reasonable probability" that the nucleic acid would be diagnostic of cancer in any way, and significantly less than a "reasonable probability" for the Pro-539 protein for which no evidence of utility whatsoever is presented. The Pro-539 protein, which protein has not been shown to be overexpressed in cancer or to have any other use, lack any "reasonable probability" of utility. Consequently, the fact pattern of Fujikawa v. Wattanasin does not apply because the level of certainty in this case is below the "reasonable probability" required by that CAFC in that decision.

This is similar to the cited Cross v. Iizuka case where specific inhibition of thromboxane synthetase was demonstrated for utility of the compounds. This is worlds apart from the current situation where no result whatsoever is shown for the claimed protein of Pro-539. No therapeutic or functional utility is even alleged other than the concept that the the Pro-539 protein may be diagnostic of cancer, for which no evidence of any utility has been provided. The closest asserted utility is for the Pro-539 nucleic acid, and this utility, for the reasons extensively discussed in the rejection, above and previously, does not carry over into the protein.

The conclusion that is reached is that it is NOT more likely than not that there is a "reasonable probability" that the asserted utility for the proteins is true.No evidence whatsoever has been presented about the claimed protein of PRO539. All of the evidence is directed towards other molecules which themselves may or may not have utility, but which do not provide specific utility for the PRO539 protein.

Conclusion and Evidence as a whole

In the decisional law, starting with the Supreme Court decision in Brenner and concluding with the Federal Circuit decision in Fisher, the caselaw has consistently required that substantial, specific and practical utility is required for the grant of a patent. The current protein PRO539 claims fall precisely in the Fisher fact pattern. In Fisher, a single piece of information was known about the claimed nucleic acids, that they were expressed in certain parts of plants. This expression was insufficient to meet the utility requirement. The current facts are worse, since the claims are not to the nucleic acids but to a putative protein whose very existence is uncertain and for which utility is solely

based upon a relationship which even Appellant's most thorough declarant, Dr. Polakis, argues is at best 80% correlative (and the art of Orntoft, Meric, Konopka and Pennica less so). Another Declarant, Dr. Smith demonstrates that the mRNA is expressed in only 8 out of 26 tumor samples. Thus, the diagnostic utility, when reviewed on the evidence as a whole, is found to lack utility based upon the substantial evidence shown in the rejection and discussed above. Therefore, the claimed invention lacks substantial and specific utility and is not enabled as lacking a use.

Written Description issues

The first issue is whether the claims comply with the written description requirement of 35 U.S.C. 112, first paragraph. In this analysis, Appellant attempts to address the structure function issue by adding the function "wherein the nucleic acid encoding the polypeptide is overexpressed in lung or colon tumor cells". This function has literally nothing to do with structure whatsoever and does not address the concern of the guidelines to have a function which delimits the sequence. Appellant also fails to note that a "representative number of species" is required. This is considered by the USPTO written description guidelines which note that in an unpredictable art, a single species is not sufficient to describe the genus.

It is the absence of any real structure function relationship and the absence of a representative number of species which supports the conclusion that there is insufficient descriptive support for the current claims. This argument rests on three grounds. First, the single sequence that is actually described is not representative of the genus of any

sequence which hybridizes under the stated conditions. Second, the claims entirely lack a structure function relationship since the function given has no ability to limit the genus of polypeptides.

Absence of a representative number of species

In the current case, the first question is what constitutes a generic claim. The genus of nucleic acids which encode polypeptides represents every possible variation which could occur in SEQ ID Nos: 7, that has 95% identity to the 830 amino acid protein. In order to provide a representative number of species, in a genus which contains literally 20^{42} (or written out fully, approximately 439,804,651,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000) different members, the court in Lilly required "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. (Lilly at page 1406)." (As a side comment, the genus size here is larger than that at issue in Deuel). Lilly continues to note that in other cases, two chemical compounds in a subgenus were insufficient to describe that genus. In the current case, Appellant argues that the single species of a single SEQ ID NO is sufficient to describe 20^{42} other sequences for which no description whatsoever is given. These sequences may be of any size or structure, so long as they are 95% identical. Appellant's analysis is flawed since there is no expectation in the instant case of insubstantial variation because the functional limitation devolves solely to the ability of

the protein to act as a reductase, but no specific substrate is required by the claims. The function provides very little guidance or information regarding the structure and does not delimit the structure in even the smallest or most miniscule possible way. So the argument by Appellant that there would be insubstantial variation is not correct since the function of "overexpression in lung or colon tumor cells" does not limit the protein in any significant way.

Appellant appears to also be making the argument that the size of the genus is not relevant. This is not found persuasive because the size of the genus is a central issue. If the genus were small, a written description rejection would be less likely, since the examples would be more representative of the genus. Here, where the genus includes 439,804,651,000,000,000,000,000,000,000,000,000,000,000,000,000,000,000 different members, literally trillions and trillions of possible molecules, none of which are disclosed or taught by Appellant, the argument that the demonstrated species is representative is not found persuasive.

How big is this genus? 4×10^{53} is certainly not a number with which most people have intuitive experience. If Appellant contacted IBM to use their fastest computer, now about 270 teraflops (or trillion calculations per second) and if each calculation was able to analyze 1 member of the claimed genus so that 270 trillion members were analyzed every second, it would take that computer about 4×10^{40} years to complete the analysis of this genus. To completely analyze the genus in 100 years using multiple versions of IBM Blue Gene L (which takes up about 1400 square feet and cost more than 100 million dollars) would require the surface area of about 5×10^{27} planets the size of the

entire earth (including the oceans). But perhaps there is some thought that the genus could be meaningfully screened in liquid form. If the screening were performed in a standard olympic swimming pool with a volume of 375,000 liters, and with a calculated molecular weight of 21,620 grams/mol at a very concentrated 25% of the solution (250 grams/liter) would yield 93,000,000 grams in our swimming pool. This would also be 4336 moles of protein. Using Avogrado's number of 6.02×10^{23} molecules/mole, would yield 2.6×10^{26} molecules in the swimming pool. This means that it would take 4,228,890,876,061,538,461,538,461 or 4×10^{24} swimming pools to fully analyze the genus. The fraction being analyzed in our single olympic size swimming pool would be 0.00000000000000000000000023 percent of the total possible members of the genus. Therefore, even screening will not detect an appreciable number of members of the genus.

Even for the smallest genus being claimed, 99%, the genus size is still $20^{8.3}$. This genus still contains 62,885,274,937 members for which Appellant has shown one.

Absence of any structure-function relationship

Second, when Appellant relies upon the analysis of the written description guidelines, this analysis is based upon the assumption that there will be insubstantial variation, as noted in many of the examples including example 9. However, Appellant's analysis is flawed since there is no expectation in the instant case of insubstantial variation because the functional limitation devolves on reductase activity. This is not like example 9, where the functional limitation involved a protein which retained adenylate cyclase activity. Adenylate cyclase is an enzyme with a defined substrate

leading to an expectation that stringently hybridizing proteins which retained the specific function of stimulating adenylate cyclase would differ insubstantially. Appellant's fundamental position fails to equate with the written description guidelines because in the guidelines, there is function correlated to the structure. The "overexpression in lung or colon tumor cells" function in Appellant's claims, however, lacks sufficient correlation with the structure of the protein since the specific changes imposed by the structure are not identified. So consonant with the case law in Lilly, Enzo and the other written description decision of the Federal Circuit, it is clear that the current claims fail to meet the written description requirement because there is no structure function relationship which limits the genus size. The guidelines require more. They require a structure function relationship where the function results in insubstantial variation in the structure.

Decisional Law

The decisional law in this area has been very consistent. The Federal Circuit in Lilly, Fiers, Rochester and many other cases has determined that the written description issue applies to situations where the definition of the subject matter of the claims fails to provide description commensurate with the genus. The most recent caselaw directly supports this rejection. As the District Court in University of Rochester v. G.D. Searle & Co., Inc. (2003 WL 759719 W.D.N.Y.,2003. March 5, 2003.) noted "In effect, then, the '850 patent claims a method that cannot be practiced until one discovers a compound that was not in the possession of, or known to, the inventors themselves. Putting the claimed method into practice awaited someone actually discovering a necessary component of the invention." This is similar to the current case since the breadth of the

current invention claims comprises compounds which were not in the possession of, or known to the inventors. In a genus that is literally incalculably immense, the specification shows at most one embodiment.

The CAFC in University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886, 1892 (CAFC 2004) noted "generalized language may not suffice if it does not convey the detailed identity of an invention." The court used an example from Enzo Biochem Inc. v. Gen-Probe Inc., 63 USPQ2d 1609, 1616 (CAFC 2002) to show why generalized language is insufficient,

> "A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its function of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. Similarly, the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity. A description of what a material does, rather than of what it is, usually does not suffice."

The current claims represent a situation that is nearly identical to the problem in Enzo, since the term "estrogen receptor" is a generic term that imposes no specific structure on the molecule. The Federal Circuit in Rochester cited with approval the District Court's comment that,

> "Tellingly, ... what plaintiff's experts'[sic] do not say is that one of skill in the art would, from reading the patent, understand what compound or compounds-which, as the patent makes clear, are necessary to practice the claimed method-would be suitable, nor would one know how to find such a compound except through trial and error ... . Plaintiff's experts opine that a person of ordinary skill in the art would understand from reading the '850 patent what method is claimed, but it is clear from reading the patent that one critical aspect of the method-a compound that selectively inhibits PGHS-2 activity-was hypothetical, for it is clear that the inventors had neither possession nor knowledge of such a compound. University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886, 1894 (CAFC 2004).

recent caselaw of the Federal Circuit, Enzo and in Rochester, the CAFC determined that such a claim does not suffice to comply with the written description requirement where no structure is present. In the application at the time of filing, there is no record or description which would demonstrate conception of the claimed proteins. Therefore, the claims fail to meet the written description requirement by encompassing proteins which are not described in the specification.

Appellant's citation to In re Wallach fails to appreciate the significant distinction in Wallach from the current case. In Wallach, the claims were to a large genus, but the genus was limited to nucleic acids which encoded a specific protein. That genus was found definite in scope not just because it could be written out as noted in the quotation given in Wallach but because the function of each of those nucleic acids would be identical. Each of the nucleic acids in the Wallach genus would encode the same exact protein. In the current case, the claims expressly and deliberately encompass different proteins, not disclosed in the specification, for which no function or description is provided.

So the claims clearly encompass sequences which were neither taught nor described by the current specification. The claims include a single species which is not representative of the full scope of the genus. Therefore, the written description rejection is maintained.

Enablement

The enablement rejection depends upon the utility rejection. Therefore, the arguments of the utility rejection extensively discussed above are subsumed into the enablement rejection.

(11) Related Proceeding(s) Appendix

The only related proceeding is the appeal in 10/033,396.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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1/17/05

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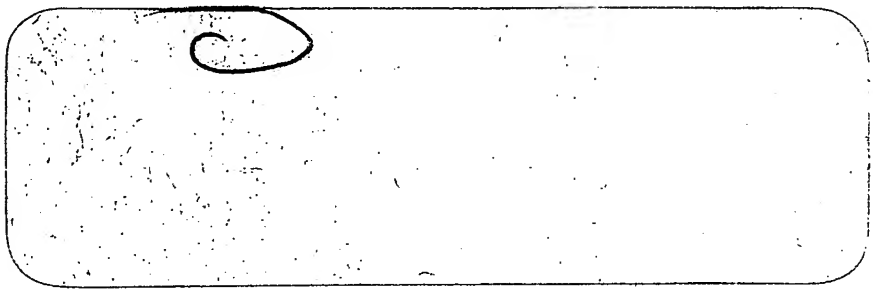

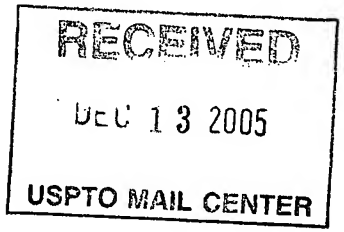

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